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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,984	07/28/2003	Guohua Chen	ARC 3119 R1	7536

7590 12/24/2008

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1616	

MAIL DATE	DELIVERY MODE
12/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/628,984	CHEN ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,6,9-19,21-35,37-47 and 49-84* is/are pending in the application.

4a) Of the above claim(s) *21-27 and 49-83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 3, 6, 9-19, 28-35, 37-47 and 84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/23/08 has been entered.

Claims 1, 4, 5, 7, 8, 20, 36 and 48 have been cancelled. Claims 21-27 and 49-83 are withdrawn. Claims 2, 3, 6, 9-19, 28-35, 37-47 and 84 are under examination.

Withdrawn rejections:

Applicant's amendments and arguments filed 9/23/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 recites the limitation "the medium molecular weight (MMW) polymer" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6 and 34 both recite 0% as a value for the amount of polymers. However claim 2 and claim 33 both positively recite the presence of, in claim 2, low and high molecular weight polymers and, in claim 33, low, medium and high molecular weight polymers. It is unclear how there can be no, 0% polymers in the injectable depot when the base claims positively recite their presence. The claims will be examined as they read on some positive amount of polymers present.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2, 3, 6, 9-19, 28-35, 37-47 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brodbeck et al. (US 6,331,311) in view of Brodbeck et al. (6,130,200), and Penco et al. (Polymer International 1998, 46, 203-216) and Ravivarapu et al. (European Journal of Pharmaceutics and Biopharmaceutics 50 (2000)263-270).

Applicant claims an injectable gel composition comprising a plurality of bioerodible, biocompatible polymers, solvent and a beneficial agent.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Brodbeck et al. teach an injectable depot gel composition comprising a biocompatible polymer such as lactic acid based polymers with a number average molecular weight of from 1,000 to 120,000, an organic solvent and a beneficial agent dispersed in the gel (Abstract and

claims 1-3 and 5). Claims 1-3 are reproduced below for Applicant's benefit (examiner added emphasis):

1. An injectable depot gel composition comprising:
a continuous, viscous gel phase comprising
a biocompatible polymer and
an organic solvent that dissolves the biocompatible polymer and forms a viscous gel;
a beneficial agent; and a separate, droplet phase dispersed in the viscous gel phase comprising
an emulsifying agent, whereby the depot gel composition is thixotropic.

2. The injectable gel depot composition of claim 1 wherein the biocompatible polymer is selected from the group consisting of polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamines, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, succinates, poly (malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and mixtures thereof.

3. The injectable depot gel composition of claim 1 wherein the biocompatible polymer is a lactic acid-based polymer.

Claim 4 recites the lactic acid based polymer has a monomer ratio of lactic acid to glycolic acid in the range of 100:0 to about 15:85 (claim 4). Clearly, Brodbeck et al. contemplate the use of biodegradable and biocompatible lactic acid based polymers. Furthermore, Brodbeck et al. teach mixtures of the lactic acid based polymers in the molecular weight range of from 1000 to 120,000 (claim 5). Thus, one interpretation of the claims is that Brodbeck et al. teach mixtures

of lactic acid based polymers of a wide molecular weight range. This would include low, medium and high molecular weight polymers in the range of claim 5. Brodbeck et al. teach the solvent is present from 20 to 95 % by weight of the combined amounts of polymer and solvent (Claim 10). Therefore the polymer must be from 5 to 80 % by weight of the composition. '311 teaches benzyl benzoate, an aromatic ester, as a solvent (column 5, lines 8-15) and alcohols, polyols, esters, carboxylic acids, ketones, aldehydes and mixtures thereof as emulsifying agents (claims 19). Brodbeck et al. teach prolonged release of the beneficial agent up to 90 days and modifying the release by adjusting the amounts of components for any given polymer and any given solvent (column 7, line 35 bridging column 8, line 53). Brodbeck et al. teach a kit for the injectable depot composition with the components (a) a biocompatible polymer and organic solvent; (b) emulsifying agent and (c) the beneficial agent (claim 27). The beneficial agent is thus separated from the solvent and mixed before use (column 8, lines 53-61). (Note: components (d)-(g) are optional in instant claim 84).

Brodbeck et al. '200 teach a gel composition for implantation of a beneficial agent to a subject comprising a biocompatible polymer, a biocompatible solvent with low water miscibility that forms a gel with the polymer and a beneficial agent (Abstract). Brodbeck et al. '200 teach poly(lactide-co-glycolide) copolymer, benzyl benzoate and a beneficial agent (Claims 1-3) wherein the copolymer has a number average molecular weight of from 1,000 to 120,000 (claim 15). A component solvent can be added such as diethyl phthalate (claim 17). Brodbeck et al. '200 teach that useful solvents are less than 7% water soluble by weight (column 12, lines 12-65). Brodbeck et al. '200 teach the use of RESOMER® RG502 AND RESOMER® RG503 for use in the invention (column 24, line 46 bridging column 25, line 5).

Penco et al. teach benzyl alcohol as a known solvent for PLGA (page 204-205, 2. synthesis).

Ravivarapu et al. teach, in the Abstract, *the concept* combining PLGA polymers that varied in their molecular weights in various ratios yielded microspheres with varied drug release profiles commensurate with the hydration tendencies of the polymers. Increasing the component of lower molecular weight 50:50 hydrophilic PLGA polymer, 8.6 kDa increased the initial drug release. A.similar microsphere formulation prepared instead with blending microspheres from individual polymers showed a similar increase. In an animal model, microspheres obtained from polymer or microsphere blends attained a faster onset of testosterone suppression as compared to microspheres from higher molecular weight 50:50 hydrophilic PLGA polymer, 28.3 kDa, alone. Ravivarapu et al. explain on page 268, right column (examiner added emphasis):

and during the 14–49 day period. PLGA polymers degrade hydrolytically giving rise to an acidic microenvironment in the particle structure [21] which enhances polymer degradation and mass loss. An acidic microenvironment is attained faster in the case of the 8.6 kDa PLGA as this polymer hydrates faster owing to its higher number of carboxylic acid endgroups. Additionally, microspheres from the lower MW polymer had a more porous internal structure which would also facilitate hydration. Thus, microspheres that contain 8.6 kDa PLGA as a combination in their structure are expected to degrade and release drug faster as compared to microspheres that are physically blended, as the hydration of the 8.6 kDa polymer will also hydrate the closely associated 28.3 kDa polymer. This may explain the higher drug release seen with polymer combination formulations at later time points. However, as the noted difference

These studies illustrated the concept of blending polymers or microspheres of varied characteristics in achieving modified drug release. It is then understood by one of ordinary skill in the art that low MW PLGA degrades faster and results and faster drug release while higher MW PLGA degrades more slowly thus manifesting a slower drug release and mixtures of the different MW polymers produces a blended release profile.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant invention and Brodbeck et al. '311 is that Brodbeck et al '311 does not expressly teach mixtures of high, medium and low molecular weight lactic acid based polymers in the injectable drug depot. This deficiency is cured by the teachings of Brodbeck et al '200 and Ravivarapu et al..

2. The difference between the instant invention and Brodbeck et al '311 is that Brodbeck et al '311 does not expressly teach benzyl alcohol as a solvent. This deficiency in Brodbeck et al'311 is cured by the teachings of Penco et al.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a mixture of high, medium and low biocompatible lactic acid based polymers as taught by Brodbeck et al '311 and use for example the lactic acid based polymers RESOMER® RG502 AND RESOMER® RG503, as suggested by Brodbeck et al '200, and in various molecular weights, as taught by Ravivarapu et al., in the gel depot of Brodbeck et al '311 and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because '311 teaches one of ordinary skill in the art mixtures of polylactides and copolymers thereof and teaches a wide range of molecular weights that encompass the instantly claimed high, medium and low molecular weight ranges that can be used to make the injectable drug depot gel composition. Ravivarapu et al. teach the benefits of combining polymers/microspheres of

different molecular weights to achieve different active release profiles. It is then merely routine optimization and judicious selection of known components in the art, for example RESOMER® RG502 AND RESOMER® RG503, for use in the composition especially when Brodbeck et al '200 teaches use of these materials for the same purpose. With respect to the limitation of systemic delivery of the beneficial agent over a duration of one year or local delivery of the beneficial agent over a duration of up to one year, that is merely routine optimization, as taught by Brodbeck et al '311, of the components to arrive at that desired release profile.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use benzyl alcohol, as taught by Penco et al., as the solvent in the composition of Brodbeck et al '311 and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because benzyl alcohol is a known solvent for PLGA polymers as taught by Penco et al. Benzyl alcohol intrinsically has the properties of water miscibility instantly claimed in the absence of evidence to the contrary (see instant claims 12-15 and 40-43).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

Applicant asserts that the Examiner's case is fatally flawed with respect to the motivation to modify Brodbeck '311 because the reference of Ravivaparu is directed to microparticles and not to any other pharmaceutical dosage forms such as injectable depot gels. Respectfully, the Examiner cannot agree. Brodbeck et al. '311 already have the broad teaching of the injectable gel depot with biocompatible lactic acid based polymers in various molecular weights which encompass that which is instantly claimed. Ravivarapu is relied upon for the teaching the *concept* that the effect of mixed populations of controlled release particles on the resulting release pattern of drugs is established in the art. The concept of mixing different molecular weight lactic acid based polymers for the use in drug delivery formulations, in this case microparticles, is taught in the art. Ravivarapu did not add a solvent to dissolve their microspheres and thus prepare a gel. However, one of ordinary skill in the art knowing the gel depot of Brodbeck '311 and the concept of mixed molecular weight polymers controlling the release of the drug contained within the matrix would have had a reasonable expectation of success in adding mixed molecular weight lactic acid based polymers to the solvent to make a gel for injection. Respectfully, the Examiner did not use hindsight reconstruction. The Examiner has combined concepts taught in the art to arrive at the instant invention. The primary reference of Brodbeck '311 teaches a genus of polymers to use in the gel depot and the art teaches the concept of using mixed molecular weight lactic acid based polymers for drug delivery.

Respectfully, Applicant's arguments are not persuasive and the Examiner maintains the rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/

Examiner, Art Unit 1616